

REMARKS

Claims 43, 47-51, 53 and 55-96 are pending.

I. Response to the Office Action

A. Response to the Rejection of Claims 43, 47-51, 53 and 55-96 under 35 U.S.C.

§103(a)

Claims 43, 47-51, 53 and 55-96 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Wahlestedt (WO 01/25248) in view of Crooke (US 5,898,031). The Applicant continues to traverse this rejection.

The Examiner argues that Wahlestedt teaches “antisense oligonucleotides having LNA and non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues.” The Examiner goes on to state that “Wahlestedt teaches that the pattern of X-Y-X can be repeated, as indicated by the integer q, and that because the integers m and p can be 0, [Wahlestedt] teaches oligonucleotides with the pattern X-Y-X-Y, meeting the limitations of the claims.” Citing Crooke, the Examiner states that it was “well-known in the art at the time the invention was made to produce oligonucleotides of different lengths and modification pattern in order to optimize their properties.” The Examiner concludes that “it would have been obvious to . . . modify the oligonucleotides taught by Wahlestedt et al. in order to produce oligonucleotides having a sequence of non-locked nucleotides of 4-20 nucleotides and would further be obvious to modify the oligonucleotides to have both and non-locked regions of specific lengths.” To support this reasoning, the Examiner cited MPEP 2144.05, regarding obviousness of ranges and optimization of ranges.

Applicant disagrees with the Examiner’s characterization of Wahlestedt and the Examiner’s conclusion regarding obviousness.

Wahlestedt’s Genus Includes Oligonucleotides Consisting of Locked Nucleotides

It is incomplete to say that Wahlestedt “antisense oligonucleotide having LNA and non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues.” At page 8 Wahlestedt describes a genus of oligonucleotides characterized

by the following formula: 5'-[X_mY_nX_p]q-3'. In this formula "X is oxy-LNA and Y is non-oxy LNA" (emphasis added). Further, both m and p are integers from "0-30", "n is an integer from 0-3", and q is an integer from 1 to 10 with the proviso that the sum of m, n and p multiplied by q is in the range of 6-100. "Non-oxy LNA", represented by Y, are defined on page 4 of Wahlestedt at lines 4-12 as including DNA, RNA, thio-LNA and amino-LNA as well as derivatives of these molecules. Thus, the oligonucleotides within the genus described by Wahlestedt can be composed entirely of various types of locked nucleotides (LNA). Therefore, Wahlestedt's genus does not simply encompass various oligonucleotide having alternating locked and non-locked nucleotides, but actually encompasses a much larger universe of molecules that includes locked nucleotides that are not oxy-LNA. Thus, if Y nucleotides that are non-locked nucleotides of any type are represented by "Y" and those nucleotides that are locked nucleotides, but not oxy-LNA (e.g., are amino-LNA or thio-LNA) are represented by "Y", then Wahlestedt's genus encompasses, for example, XY_{YY}XY_{YY}X, XY, YX_{YY}Y_{YY}X, XYY, YYX and a huge number of other patterns. Thus, it is incomplete to say that "antisense oligonucleotide having LNA an non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues."

The Examiner has not identified an "expressly described species or subgenus" within Wahlestedt

The Examiner's obviousness rejection appears to be based on the argument that the presently claimed oligonucleotides are a subgenus within the genus that is disclosed by Wahlestedt and that the claimed oligonucleotides could be arrived at by "routine optimization" of that which is disclosed by Wahlestedt.

The Examiner's analysis is flawed. First, as MPEP 2144.08 explains the "patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103". The courts have made clear that the fact that a claimed subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992); *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

Second, as also explained in MPEP 2144.08, the first step in obvious analysis is determining the scope and content of the prior art (emphasis added):

In the case of a prior art reference disclosing a genus, Office personnel should make findings as to:

- (A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus;
- (B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus;
- (C) the predictability of the technology; and
- (D) the number of species encompassed by the genus taking into consideration all of the variables possible.

The MPEP goes on to explain that: "Once the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus are identified, Office personnel should compare it to the claimed species or subgenus to determine the differences. Through this comparison, the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed." (emphasis added).

In the present case, the Examiner began the obviousness rejection by stating that Wahlestedt "teaches oligonucleotides with the pattern X-Y-X-Y, meeting the limitations of the claims". As the Applicant explained previously Wahlestedt does not disclose such an oligonucleotide. The only species disclosed by Wahlestedt are limited to one having the pattern X-Y-X where all X are DNA and Y-X-Y-X-Y-X-Y-X-Y, which all X are DNA (see page 10, lines 9-10). Thus, the Examiner's analysis of the prior art has not included identification of "the closest disclosed species or subgenus" in the cited prior art because the Examiner relies on a undisclosed species. The XYXY¹ pattern identified by the Examiner is merely one of the many, many possible oligonucleotide patterns within the genus disclosed by Wahlestedt. The Examiner's obviousness argument is improper because it is based on supposed "routine optimization" of an embodiment X-Y-X-Y (where all Y are non-locked nucleotides) that is

¹ In fact, even if the XYXY pattern were disclosed, it would not necessarily be an alternating pattern of locked and non-locked nucleotides because, as explained above, Wahlestedt defines Y to include locked nucleotides such as thio-LNA and amino LNA. Thus, XYXY equally could represent all locked nucleotides.

simply not disclosed by Wahlestedt. It is not proper to base an obviousness rejection on "routine optimization" of a range in an embodiment that is not even disclosed in the cited prior art.

The importance of identifying the closest disclosed species or subgenus at the outset of obviousness analysis was recently emphasized by the Federal Circuit in a case concerning the requirements for establishing a case of *prima facie* obviousness based on chemical similarity in the context of a pharmaceutical invention *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007). The court in *Takeda* held that order to establish a *prima facie* case in such a situation it is "necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner" and that "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." *Takeda* at 1356-57 (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added). Moreover, in *Takeda*, the court found that the argument for obviousness failed because it relied on selecting one of the many compounds disclosed in the prior art reference as a lead compound where there was reason to believe that the compound would not have been selected as the lead compound. *Takeda* at 1360. See also *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals*, 471 F.3d 1369 (Fed. Cir. 2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as lead compound).

It would not be proper to base an obviousness rejection Wahlestedt's disclosure of 5'-[X_mY_nX_p]_q-3'

It would also not be proper for the Examiner to have based the obviousness rejection on the disclosure of Wahlestedt's genus, i.e., 5'-[X_mY_nX_p]_q-3'. As discussed above, this genus encompasses a vast number of oligonucleotides with varying patterns of locked nucleotides non-locked nucleotides as well as oligonucleotides that are entirely composed of locked nucleotides. Modifying the oligonucleotides of this very broad genus would require making particular choices for numerous variables and cannot be considered "routine optimization".

Applicant : Charlotte Albaek Thru et al.
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Summary

It is respectfully submitted that the conclusion that the rejected claims are obvious based on the reasoning set forth in the Office Action, is reached by not applying the proper standards for determining obviousness under 35 U.S.C. § 103(a). In view of the foregoing remarks, the applicants therefore respectfully request that the Examiner reconsider the rejection of claims 43, 47-51, 53 and 55-96 made under 35 U.S.C. § 103(a). It is submitted that the rejection has not provided any adequate reason showing why it would have been obvious for the person skilled in the art to make oligonucleotides according to claims 43, 47-51, 53 and 55-96. Applicant therefore respectfully ask that the rejection made under 35 U.S.C. § 103(a) be withdrawn upon reconsideration.

III. Conclusion

Based on the foregoing, the applicants believe that the rejections have been overcome. It is respectfully submitted that the application should be found in condition for allowance, and an early notice toward that end is earnestly solicited.

Enclosed is a Enter \$ amount check for excess claim fees and a Enter \$ amount check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050 referencing Attorney Docket 22460-0010001.

Respectfully submitted,

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/Anita L. Meiklejohn/

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945